

Design and Synthesis of Highly Selective Ionophores for Lithium Ion Based on 14-Crown-4 Derivatives for an Ion-Selective Electrode

Koji Suzuki,^{1,*} Hiroyuki Yamada,¹ Kazunari Sato,¹ Kazuhiko Watanabe,¹ Hideaki Hisamoto,¹ Yoshito Tobe,¹ and Kazuya Kobiros²

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223, Japan, Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka 560, Japan, and Department of Science, Niihama National College of Technology, 7-1 Yagumo, Niihama, Ehime 792, Japan

Highly Li⁺-selective ionophores based on 14-crown-4 derivatives were designed and synthesized, and the relationship of their molecular structures and ion selectivities was investigated in order to obtain a highly Li⁺-selective electrode. The ion selectivities were examined with 11 kinds of 14-crown-4 derivatives, which were prepared according to the proposed two types of Li⁺ ionophore models. Excellent Li⁺-selective ionophores were obtained by introducing a bulky "block" subunit into the ethano-bridge section of the base crown ring, which effectively prevents the formation of a 2:1 or 3:1 sandwich-type complex consisting of the crown ether and cations larger than Li⁺. The best Li⁺/Na⁺ selectivity (more than 1000) was obtained for the electrode using the 14-crown-4 derivative with a bulky decalin subunit. These results offer the general ion selectivity features of 14-crown-4-based compounds.

INTRODUCTION

A highly Li⁺-selective electrode is desired in medical and clinical fields, because some lithium salts such as Li₂CO₃ have been effectively used as medicine for manic-depressive patients; hence continuous monitoring of Li⁺ is sometimes required to control the Li⁺ concentration in the human body.¹ The primary interference is Na⁺ in most cases for Li⁺ measurements; therefore, a Li⁺-selective electrode with a high Li⁺/Na⁺ selectivity is the primary subject.² One of the recognized ways for obtaining a highly Li⁺-selective electrode is to create and utilize an excellent Li⁺-selective neutral ionophore as an ion-sensing component of the ion-selective electrode. In the past, several highly Li⁺-selective electrodes which exhibited a Li⁺/Na⁺ selectivity over 100 were developed using a noncyclic polyether diamide,³ a phenanthroline derivative,⁴ and crown ether compounds⁵⁻¹¹ (for a review, see ref 11). However, all the electrodes developed to date have

never successfully been able to monitor Li⁺ in the serum of manic-depressive patients.

In general, when considering the coordination feature of alkali metal cations such as Li⁺ as the guest cation upon the binding atom of the host ionophore molecule, it is known that the oxygen atom is more effective than nitrogen or sulfur atoms based on the hard-soft and acid-base (HSAB) concept.¹² There are several types of oxygen that act as a binding group for the cation, e.g., esters, ethers, phosphates, amides, etc. In the case of an ionophore that has strongly binding oxygen atoms that exist in a phosphate or amide group, divalent alkaline earth metal cations such as Ca²⁺ and Ba²⁺ are also susceptible to binding; therefore, the monovalent cation selectivity of the ionophore molecule relative to that for divalent cations must be poor. Hence, either an ester- or an ether-type oxygen is considered to be the best binding site for the monovalent alkali metal cation-selective ionophore. Among them, the most typical ether-type ionophores are the well-known crown ethers. As for Li⁺, crown ethers with a 13-16-membered ring are adequate for Li⁺ coordination.⁵⁻⁷ The cavity of the 14-crown-4, especially, has the best fit for the Li⁺ as a 1:1-type ionophore-cation complex,¹³ and some 14-crown-4 derivatives have actually already been used for the Li⁺-sensing component for ion-selective electrodes.^{5,7-10,13} However, most crown compounds also generally form a 2:1 or 3:1 ionophore-cation complex with larger size cations. In fact, using this phenomenon, some highly specific ion-selective bis(crown ethers) have been developed successfully as Na⁺- and K⁺-selective ionophores.¹⁴ In order to form only a 1:1-type complex, additional factors must be considered.

To obtain a highly Li⁺-selective ionophore, here we considered two models as shown in Figure 1. They both are assumed to form 1:1 ionophore-Li⁺ complexes. The model I type molecule has one bulky subunit or side chain that blocks the coordination of this molecule to a larger sized cation. That is, this bulky subunit or side chain prevents the formation of a 2:1 or a 3:1 sandwich-type ionophore-cation complex. Consequently, this type of molecule is expected to have a

* Author to whom correspondence should be addressed.

¹ Keio University.

² Osaka University.

³ Niihama National College of Technology.

(1) Amdisen, A. D. *Handbook of Lithium Therapy*; MTP Press: Lancaster, U.K., 1986.

(2) Ammann, D. *Ion-Selective Microelectrodes*; Springer-Verlag: New York, 1986; Chapter 7.

(3) Metzger, E.; Ammann, D.; Asper, D.; Simon, W. *Anal. Chem.* 1986, 58, 132.

(4) Sugihara, H.; Okada, T.; Hiratani, K. *Chem. Lett.* 1987, 2391.

(5) Kimura, H.; Oishi, O.; Murata, T.; Shono, T. *Anal. Chem.* 1987, 59, 2331.

(6) Tohda, T.; Sasakura, H.; Suzuki, K.; Shirai, T. *Proc. Chem. Soc. Jpn. Annu. Meet.* 54th, Tokyo, Japan, 1987; p 473.

(7) Attiyat, A. S.; Christian, G. D.; Xie, R. Y.; Wen, X.; Bartach, R. A. *Anal. Chem.* 1988, 60, 2561.

(8) Suzuki, K.; Hayashi, K.; Tohda, K.; Watanabe, K.; Ouchi, M.; Hakushi, T.; Inoue, Y. *Anal. Lett.* 1991, 24, 1085.

(9) Katak, R.; Nicholson, P. E.; Parker, D.; Covington, A. *Analyst* 1991, 116, 135.

(10) Kobiros, K.; Tobe, Y.; Watanabe, K.; Yamada, H.; Suzuki, K. *Anal. Lett.* 1993, 26, 49.

(11) Umezawa, Y. *Handbook of Ion-Selective Electrodes: Selectivity Coefficients*; CRC Press: Boca Raton, FL, 1990.

(12) Pearson, R. G. *J. Chem. Educ.* 1968, 45, 643.

(13) Olsner, U. *J. Am. Chem. Soc.* 1982, 104, 4006.

(14) Tamura, H.; Shono, T.; Kimura, K. *Anal. Chem.* 1982, 54, 1224.

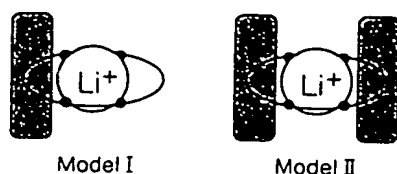


Figure 1. Li^+ -selective ionophore model molecules, types I and II: cyclic molecules with four coordination sites (●, donor oxygen) and one or two bulky blocking walls.

high selectivity for a suitable specific ion as a 1:1 ionophore-cation complex form. For the model II type molecule, two bulky subunits or side chains are introduced into the cyclic molecule which have effective roles as double "blocking walls" for the formation of the sandwich-type ion complex.

On the other hand, as another idea for a Li^+ -selective ionophore model molecule based on a crown ether, we can also propose the "lariat-type molecule", which has one or two oxygens in the side chain(s) attached to the cyclic molecule,¹⁵ which can increase the complex's stability by adding to the coordination number as well as offering a tridimensional coordination space for a suitably specific ion. However, this idea did not prove to be an effective Li^+ -selective ionophore design,¹⁶ because Li^+ prefers to form a complex with a coordination of 4. The basic 14-crown-4 itself already has four coordination sites, which is an adequate coordination number for the small cation. In fact, most highly Li^+ -selective ionophores developed to date have coordination numbers of 4.³⁻⁶

In this report, 11 types of 14-crown-4 derivatives were designed and synthesized (compounds B–L in Figures 2 and 4) based on the two effective ionophore models (see Figure 1), and the relationship between the synthesized ionophore chemical structures and their ion selectivity was discussed in detail after evaluating them as the ion-sensing component for a potentiometric Li^+ -selective electrode. As a result, a Li^+ -selective electrode was obtained which had a very high Li^+ -selectivity ratio (over 1000) against all alkali metal and alkaline earth metal ions except Li^+ . An electrode based on the 14-crown-4 derivative E (see Figure 2), was successfully applied to Li^+ measurement of artificial serum samples which included 0.5 mM Li^+ and 150 mM Na^+ (the measurement error was 3.4% in the case where the background Na^+ concentration varies in the range from 100 to 150 mM).

The knowledge obtained of the structural factors in the Li^+ selectivity of 14-crown-4 compounds supplied both an important concept and information in relation to the host-guest chemistry.

EXPERIMENTAL SECTION

Reagents. Reagents of the highest grade commercially available were used for the syntheses of new compounds and the preparation of the aqueous test electrolytes. The distilled and deionized water used had a resistivity of greater than $1.5 \times 10^7 \Omega \text{ cm}$ at 25 °C. The electrode membrane solvent bis(1-butylphenyl) adipate (BBPA) was purchased from Fluka AG, Buchs, Switzerland. Poly(vinyl chloride) (PVC, high molecular weight type) used as the electrode membrane material was obtained from Sigma, Chemical Co., St. Louis, MO.

Synthesis of 14-Crown-4-Derivatives. The chemical structures of all synthesized 14-crown-4 derivatives as Li^+ -selective ionophores are shown in Figures 2 and 4. Compound A (2,3,9,10-dibenzo-14-crown-4) was synthesized according to the reported procedure.¹³ B (2,2,3,3-tetramethyl-9-tetradecyl-1,4,8,11-tetraoxatricyclo[12.4.0.1¹⁴]decane), C ((1R,14S,16R,18R)-1,17,17-trime-

thyl-7-tetradecyl-2,6,9,13-tetraoxatricyclo[12.4.0.1¹⁴]octadecane), D (7-tetradecyl-2,6,9,13-tetraoxatricyclo[12.4.3.0^{1,14}]henicosane), and E (7-tetradecyl-2,6,9,13-tetraoxatricyclo[12.4.4.0^{1,14}]docosane) were synthesized by the following procedures. After the addition of 2.0 g (7.7 mmol) of 1,2-hexadecanediol and 0.56 g (23 mmol) of sodium hydride to 30 mL of N,N' -dimethylformamide (DMF), the mixture was stirred at 50 °C for 30 min. Allyl bromide (2.25 g) was then added to the reaction mixture, and the mixture was stirred at 80 °C for 24 h. After evaporation of DMF, the resulting residue was extracted three times with chloroform. The organic phase was evaporated, and the obtained residue was purified by silica gel column chromatography with hexane-ethyl acetate (9:1) as the eluent to yield 5-tetradecyl-4,7-dioxo-1,9-decadiene (product 1; 431 mg, 16.5% yield). Product 1, 43 mg (1.15 mmol) of NaBH_4 , and 217 mg (1.53 mmol) of boron trifluoride ethyl ether complex ($\text{BF}_3(\text{C}_2\text{H}_5)_2$) were added to 30 mL of tetrahydrofuran (THF), and the mixture was stirred at ambient temperature for 24 h. After addition of small amounts of deionized water, 36 mg (0.9 mmol) of NaOH and 30% H_2O_2 aqueous solution (0.3 mL) were added to the reaction mixture; the resultant mixture was stirred for 2 h. The dihydroxy product, 5-tetradecyl-4,7-dioxo-1,10-decanediol (product 2), was extracted from the reaction mixture with ethyl acetate and purified by silica gel column chromatography with hexane-ethyl acetate (1:4) as the eluent (71 mg, 14% yield).

Using 2 and *p*-toluenesulfonyl chloride, the ditosylate adducts of 3 (576 mg, 58% yield) were prepared according to the reported procedure.¹⁷ 3, 576 mg (0.84 mmol), and 143 mg (0.84 mmol) of *cis*-9,10-dihydroxydecalin prepared according to procedures reported previously¹⁸ were added into 40 mL of DMF and refluxed for 72 h. One of the final products, E, was extracted from the reaction mixture with ethyl acetate and purified by silica gel column chromatography with hexane-ethyl acetate (15:1) as the eluent (yield: 1.3 mg, 0.3%). B (yield: 28.7 mg, 4.3%), C (yield: 12.9 mg, 3.6%), and D (yield: 15.4 mg, 2.4%) were prepared from 3 and one of the following appropriate materials: pinacol (173 mg, 1.46 mmol), (1R,2R,3S,5R)-(-)-pinanediol (114 mg, 0.67 mmol), or *cis*-8,9-dihydroxynonalin (200 mg, 1.28 mmol) according to the same procedures for the synthesis of E.

G ((1R,14S,16R,18R)-1,7,7,8,8,17,17-heptamethyl-2,6,9,13-tetraoxatricyclo[12.4.0.1¹⁴]octadecane) was synthesized according to procedures reported elsewhere.¹⁹ F (2,2,3,3,9,9,10,10-octamethyl-1,4,8,11-tetraoxacyclotetradecane; yield: 16.0 mg, 5.1%), H (7,7,8,8-tetramethyl-2,6,9,13-tetraoxatricyclo[12.4.3.0^{1,14}]henicosane; yield: 3.3 mg, 1.8%), I (7,7,8,8-tetramethyl-2,6,9,13-tetraoxatricyclo[12.4.4.0^{1,14}]docosane; yield: 13.0 mg, 3.8%), and J ((2R,3R)-2,3-(dibenzoyloxymethyl)-9,9,10,10-tetramethyl-1,4,8,11-tetraoxacyclotetradecane; yield: 37.4 mg, 13.5%) were respectively prepared from pinacol (1.0 mmol, 0.12 g; Tokyo Chemical Industry Co., Japan), *cis*-8,9-dihydroxynonalin (86.4 mg, 0.55 mmol), *cis*-9,10-dihydroxydecalin (157 mg, 0.92 mmol), and (+)-1,4-di-*O*-benzyl-D-threitol (167 mg, 0.55 mmol) by reacting with 4,7-dioxo-5,5,6,6-tetramethyldecane-1,10-diol bis-(*p*-toluenesulfonate) (1 equiv relative to these diol derivatives) according to the same method used to obtain G. *cis*-8,9-dihydroxynonalin was prepared by the same method used for the synthesis of *cis*-9,10-dihydroxydecalin.¹⁸

K (13,13-diethyl-8,11,15,18-tetraoxaspiro[5.13.1^{1,4}]-2-icosene) and L (10,10-diethyl-2,2,4,4-tetramethyl-1,5,8,12-tetraoxacyclotetradecane) were synthesized according to the following procedures. After addition of 0.65 g (4.89 mmol) of 3,3-dihydroxypentane and 0.35 g (14.6 mmol) of sodium hydride to 30 mL of THF, the mixture was stirred at 80 °C for 30 min. Three grams of 2-(benzyloxy)ethanol *p*-toluenesulfonate (9.7 mmol) dissolved in 5 mL of THF, which was prepared from (benzyloxy)-ethanol, was added dropwise to the reaction mixture, and the mixture was stirred at 80 °C for 16 h. After evaporation of the THF, the resulting residue was extracted three times with chloroform. The organic phase was evaporated, and the obtained residue was purified by silica gel column chromatography with hexane-ethyl acetate (9:1) as the eluent to yield a dibenzyl

(15) Gokel, G. W.; Dishong, D. M.; Diamond, C. J. *J. Chem. Soc., Chem. Commun.* 1980, 1053.

(16) Yamada, H. M. Sci. Thesis, Keio University, Yokohama, Japan, 1993.

(17) Wentworth, S. E.; Sciaraffa, P. L. *Org. Prep. Proced.* 1969, 1, 225.

(18) Kohiro, K.; Matsuoka, T.; Takada, S.; Kakiuchi, K.; Tobe, Y.; Odaira, Y. *Chem. Lett.* 1986, 713.

(19) Watanabe, K.; Nakagawa, F.; Yamada, H.; Hisamoto, H.; Suzuki, K. *Anal. Chem.*, in press.

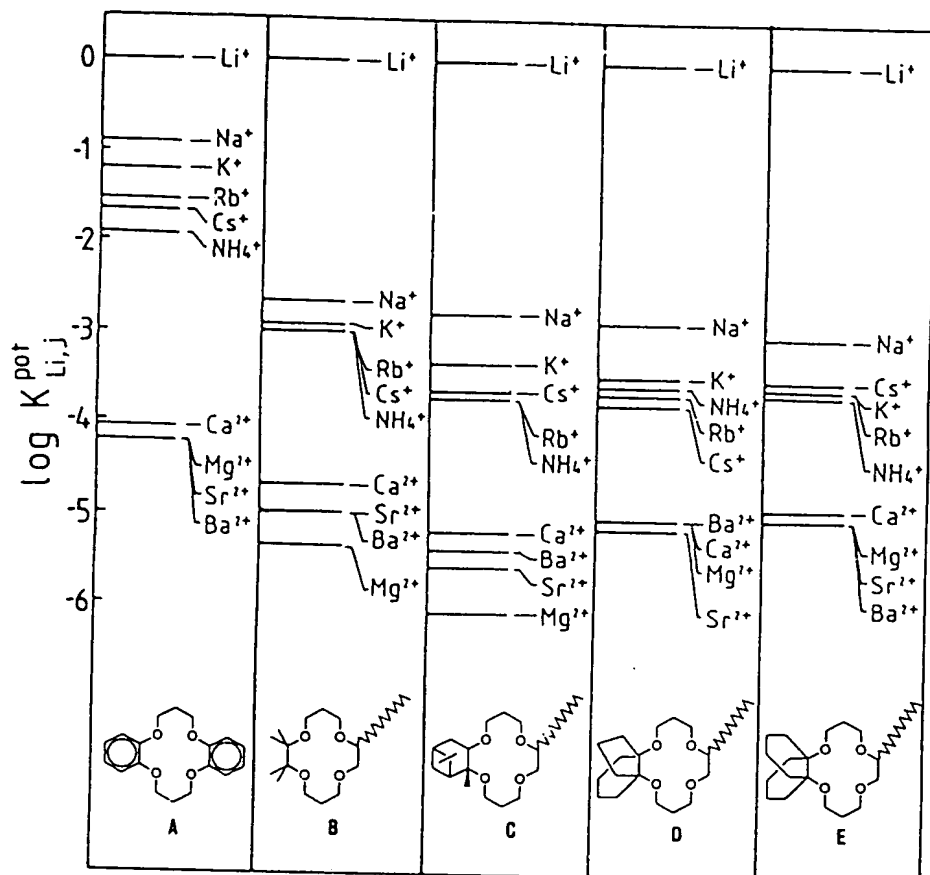


Figure 2. Ion selectivity factors ($\log K_{Li,j}^{pot}$; j = Interfering Ion) of the electrodes based on the model I type Li^+ -selective ionophores (B–E).

product, 1,9-(dibenzoyloxy)-5,5-diethyl-3,7-dioxanonane (product 4; 1.34 mg, 72.8% yield). 4 (1.34 mg, 3.55 mmol) was dissolved in 3 mL of methanol and catalytically reduced to a dihydroxy product (product 5) with 0.67 g of 10% palladium carbon powder under a 1-atm hydrogen atmosphere for 10 h at ambient temperature (yield: 1.00 g, 92.6%). A ditosyl adduct of 5, 5,5-diethyl-3,7-dioxa-1,9-nonandiol ditosylate (product 6), was prepared with 5 (1.00 g, 4.54 mmol) and *p*-toluenesulfonyl chloride (2.59 g, 13.6 mmol) according to previously reported procedures (yield: 1.36 g, 56.8%).¹⁴ K (yield: 53.3 mg, 9.4%) and L (yield: 26 mg, 9.1%) were prepared from 5-norbornene-2,2-dimethanol (263 mg, 1.70 mmol) and 2,4-dimethyl-2,4-pentanediol (120 mg, 0.90 mmol) using 6 (1 equiv relative to these diols) according to the same method used for G. Reversed-phase HPLC (ODS, methanol) was used for the final purification of all of these synthesized ionophores.

Satisfactory spectral and analytical data (¹H-NMR, IR, and elemental analysis) were obtained for all of the synthesized ionophores with the results presented below. For B (white powder). Anal. Calcd for $\text{C}_{28}\text{H}_{54}\text{O}_4$ (456.75): C, 73.63; H, 12.36. Found: C, 73.50; H, 12.20. For C (white powder). Anal. Calcd for $\text{C}_{32}\text{H}_{60}\text{O}_4$ (508.83): C, 75.54; H, 11.89. Found: C, 75.35; H, 11.70. For D (white powder). Anal. Calcd for $\text{C}_{31}\text{H}_{58}\text{O}_4$ (494.80): C, 75.25; H, 11.82%. Found: C, 75.15; H, 11.75. For E (white powder). Anal. Calcd for $\text{C}_{32}\text{H}_{60}\text{O}_4$ (508.83): C, 75.54; H, 11.89. Found: C, 75.32; H, 11.74. For F (white powder). Anal. Calcd for $\text{C}_{18}\text{H}_{36}\text{O}_4$ (316.48): C, 68.31; H, 11.47. Found: C, 68.20; H, 11.40. For H (white powder). Anal. Calcd for $\text{C}_{21}\text{H}_{36}\text{O}_4$ (354.53): C, 75.25; H, 11.82. Found: C, 75.05; H, 11.55. For I (white powder). Anal. Calcd for $\text{C}_{27}\text{H}_{40}\text{O}_4$ (368.56): C, 75.54; H, 11.89. Found: C, 75.35; H, 11.60. For J (colorless oil). Anal. Calcd for $\text{C}_{30}\text{H}_{44}\text{O}_4$ (500.79): C, 71.97; H, 8.86. Found: C, 71.80; H, 8.70. For K (colorless oil). Anal. Calcd for $\text{C}_{20}\text{H}_{34}\text{O}_4$ (338.49): C, 70.97; H, 10.12. Found: C, 70.85; H, 10.00. For L (colorless oil). Anal. Calcd for $\text{C}_{18}\text{H}_{36}\text{O}_4$ (316.48): C, 68.31; H, 11.47. Found: C, 68.08; H, 11.38.

Electrode Preparation and emf Measurements. Ion-sensitive membranes of the PVC matrix type were prepared according to the procedures previously described.²⁰ The polymeric membrane compositions were 2–3% (by weight) ionophore, 70% membrane solvent BBPA, 1% (ca. 20–30 mol % relative to the ionophore) potassium tetrakis(*p*-chlorophenyl)borate (KTCPB, Dojindo Laboratories, Kumamoto, Japan), and 26–27% PVC. The membrane thickness was ca. 100 μm . A 6-mm-diameter circle was cut from the prepared membrane and placed on the tip of the PVC ion-selective electrode body assembly (Liquid Electrode Membrane Kit, DKK Co., Ltd., Tokyo, Japan). The prepared electrodes were immersed in 0.1 M LiCl solution for over 24 h for preconditioning before use. The external reference electrode was a double-junction-type Ag–AgCl electrode (HS-305DS, Toa Electronics, Ltd., Tokyo, Japan). The electrode response potential (emf) measurements were performed according to the reported procedure at $25 \pm 0.5^\circ\text{C}$ using the electrochemical cell system,²⁰

Ag; AgCl,

3 M KCl|0.3 M NH_4NO_3 |test solution|membrane|0.1 M LiCl,

AgCl; Ag

All test solutions were made from chloride salts without any pH-adjusting buffer reagent.

The selectivity coefficients k_{ij}^{pot} , where i is the primary ion (Li^+) and j is the interfering ion were calculated from the response potentials in an alkali metal or alkaline earth metal chloride solution mainly using the separate solution method (SSM; $i = j = 0.1$ M) and partially using the fixed interference method (FIM; $j = 0.15$ M) according to the recommendations of IUPAC and JIS.^{21,22}

Determination of Lipophilicities of Ionophores. The lipophilicities of several synthesized ionophores, $\log P_{o/w}$ (P_o/w ,

(20) Suzuki, K.; Tohda, K.; Aruga, H.; Matsuzoe, M.; Inoue, H.; Shirai, T. *Anal. Chem.* 1988, 60, 1714.

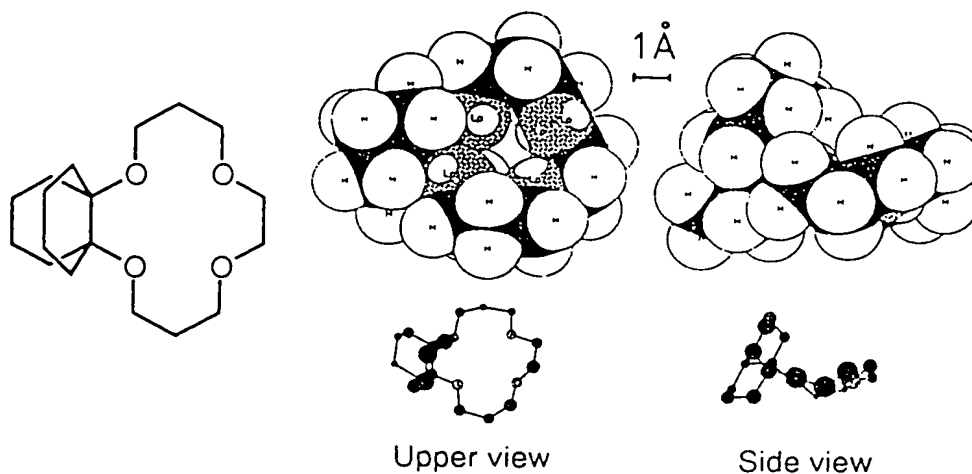


Figure 3. Space-filling (CPK) model views of decalino-14-crown-4.

distribution coefficient between organic liquid and water), were determined with the R_f values of reversed-phase thin-layer chromatography (RP-TLC) according to the method reported by Simon et al.²³ The RP-TLC used octadecylsilane-modified silica plates (KC18F, Whatman) that were cut to a length of 20 cm and developed chromatographically with ethanol-water (9:1) as the mobile phase.

RESULTS AND DISCUSSION

The chemical structures of 14-crown-4 derivatives designed and synthesized based on the model I type molecule (see Figure 1) are shown in Figure 2 (B–E). The ion selectivity of the electrodes using these derivatives are also given in Figure 2. These all obviously exhibit higher Li^+ selectivity compared with the electrode based on dibenzo-14-crown-4 (A), which has a normal plain ring structure distinct from the other 14-crown-4 derivatives of B–E. In the model I type ionophores B–E, the long alkyl chain of *n*-tetradecyl was introduced, which raised the lipophilicity over 10^{11} ($\log P_{o/w} \geq 11$) in the distribution ratio between oil and water, which is required to apply them as ion-sensing components for ion-selective electrodes in practical use (theoretical use requires that $\log P_{o/w} \geq 11.3$ for the electrode to be used for continuous measurement of whole blood samples with a lifetime of 30 days).²⁴ Consequently, all ionophores B–E have a very high lipophilicity, $\log P_{o/w} \geq 14$ ($\log P_{o/w}$: B, 14.0 ± 0.2 ; C, 14.9 ± 0.2 ; D, 16.3 ± 0.3 ; E, 16.5 ± 0.3 (cf. I, 9.3 ± 0.2)).

As the most simple "block" subunit, tetramethylethane was chosen and synthesized as a model I type ionophore, B. As a result, the electrode based on B showed Li^+/Na^+ selectivity of $\log k_{\text{Li}^+/\text{Na}^+}^{\text{pot}} = -2.6$, which was a value higher than expected. The worth of this remark is that the introduction of this simple bulky subunit, tetramethylethane, into the base 14-crown-4 yields a Li^+/Na^+ selectivity over 300, whereas the basic 14-crown-4, A, exhibited a selectivity of only ~ 10 .

The selectivity difference between the 14-crown-4-based compounds A and B was caused by the following two structural factors: (i) the flexibility/rigidity of the base crown ring; (ii) the steric position and bulkiness of the subunit in the base ring. These are important factors which must be considered in the designing of all ionophores based on crown

ether compounds. The 14-crown-4 itself cannot be formed as a stable 1:1 complex with Na^+ or K^+ , which has a larger diameter than that of Li^+ , because the donor number and the cavity size are too small for these cations. However, in the case where the 14-crown-4 makes a stable 2:1 complex with these large-sized cations, the four electron donor oxygens must face toward the same direction as much as possible (either the upper or lower position against the cavity plane of the 14-membered ring). This is mainly concerned with structural factor i. On the other hand, structural factor ii is related to the "block effect", which also prevents the formation of a stable sandwich-type complex with a large-sized cation. In this case, it is important that the bulky subunit or side chain hinder a large-sized cation from getting too close to the donor oxygen which exists very close to the block subunit or side chain in the crown ring. When either factor i or factor ii is being considered, A has a more favorable structural feature in the sandwich-type complexation with a large-sized cation than that with B. Thus, the large resulting Li^+/Na^+ selectivity difference between A and B is understandable.

The pinane group is a bulkier and more rigid element compared to the tetramethylethane subunit. If the high Li^+/Na^+ selectivity were simply caused by the steric hindrance of the host molecule to the guest cation, the use of a bulkier subunit would be considered more effective for obtaining the desired selectivity feature, which is concerned with the above-mentioned factor ii. The electrode using C, which has a pinane subunit in the crown ring, exhibited higher Li^+/Na^+ selectivity compared to that of the electrode based on B. Furthermore, the electrodes using D and E, which both have a bulky bicyclic subunit such as cyclohexano- or cyclopentanoethane, also exhibit excellent Li^+/Na^+ selectivity. Especially, the 14-crown-4 derivative, E, which has a decalin subunit, has Li^+ selectivity ratios of over 1000 against all alkali metal and alkaline earth metal ions except Li^+ . As shown in Figure 3, the CPK molecular model examination of this molecule suggests that the two cyclohexyl rings in the decalin subunit are almost perpendicular to the base ring, so that two effective bulky blocking walls are formed above and below the crown ring. This excellent Li^+/Na^+ selectivity did not vary when a long alkyl chain such as the *n*-tetradecyl group was introduced, nor did it vary at the opposite ethano-bridge section of the base 14-crown-4.¹⁰

The chemical structures of ionophore molecules designed and synthesized on the basis of the model II type molecules are shown in Figure 4 (F–I), which have two bulky subunits or side chains in the base 14-crown-4. Among them, all four compounds from F to I possess a tetramethyl ethano bridge

(21) IUPAC Recommendation for Nomenclature of Ion-Selective Electrodes. *Pure Chem.* 1976, 48, 129.

(22) JIS K-0122, Japanese Standards Association, Tokyo, 1981.

(23) Laubli, M. W.; Dinton, O.; Pretsch, E.; Simon, W. *Anal. Chem.* 1985, 57, 2756.

(24) Linten, O.; Spichger, U. E.; Chaniotakis, N.; Gehrig, P.; Rusterholz, B.; Morf, W. E.; Simon, W. *Anal. Chem.* 1991, 63, 596.

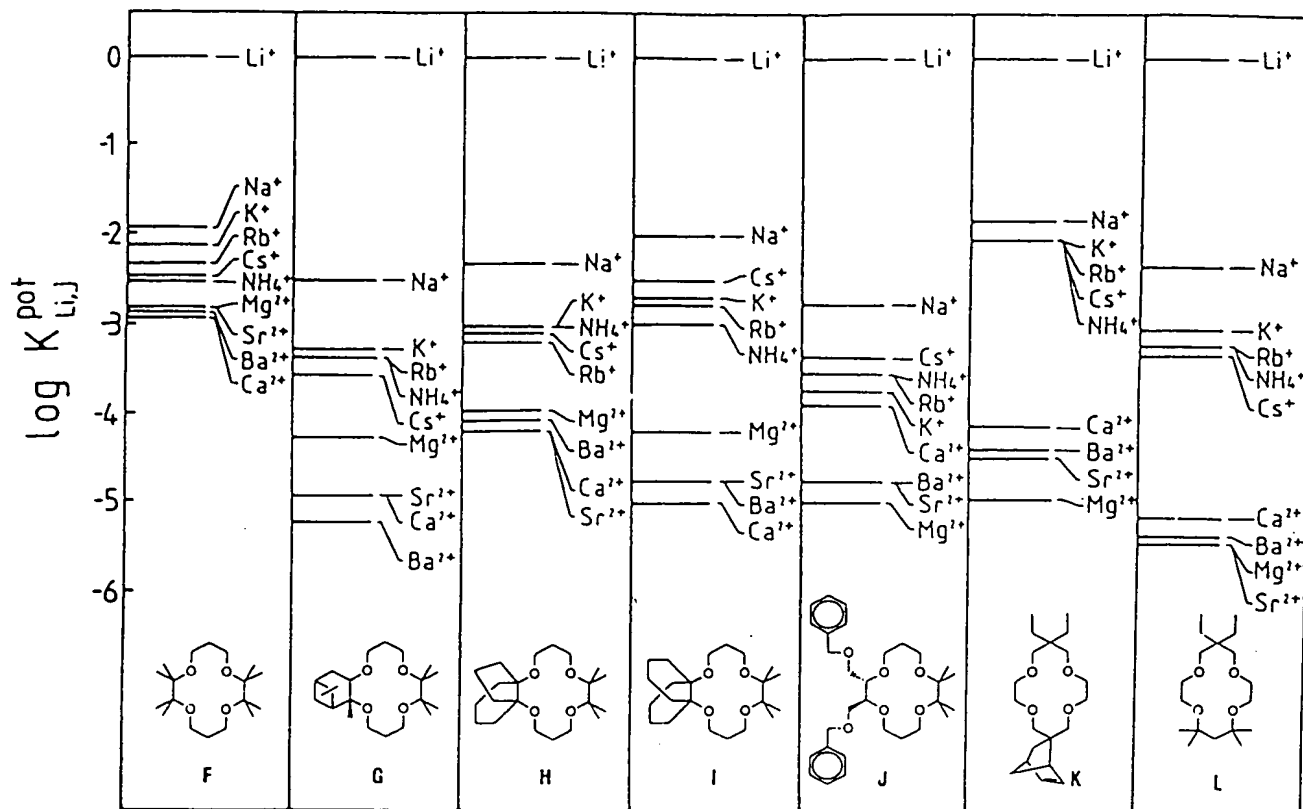


Figure 4. Ion selectivity factors ($\log K_{Li,J}^{pot}$; J = interfering ion) of the electrodes based on the model II type Li^+ -selective ionophores (F–L).

and one other bulky subunit in the opposite ethano-bridge section of the base crown ring. The latter bulky subunits correspond to those having the four model I type compounds, B–E (see Figure 2). In addition, K and L both have two bulky subunits at the two propylene-bridge sections in the base 14-crown-4. These two compounds were prepared to compare the effectiveness of a bulky subunit in a different position of the base crown ring.

We expected the Li^+ selectivity against other alkali metal ions of these compounds based on the ionophore model II to be much better than those of the model I type ionophores. As shown in Figure 4, the electrodes based on the former four compounds F–I all exhibited high Li^+ selectivities of over 80 ($\log K_{Li,J}^{pot} \leq -1.9$) against all alkali metal and alkaline earth metal ions except Li^+ . However, when the ion selectivities of the electrodes using the four model II type compounds of F–I (Figure 4) were compared with those of the corresponding model I type molecules B–E (Figure 2), the former model II type molecules exhibited a little poorer Li^+/Na^+ selectivity ($\log K_{Li,Na}^{pot} = -1.9$ to -2.5) than the latter model I type molecules ($\log K_{Li,Na}^{pot} = -2.6$ to -3.1). These results suggest that the introduction of excess bulky subunits as blocking walls for large-sized cations not only prevents the formation of sandwich-type ionophore–cation complexes but also causes formation of a simple 1:1-type Li^+ complex. In fact, the emf values 0.1 M Li^+ measured with the electrodes using F–I were all observed to be smaller than those with B–E, whereas the emf values for 0.1 M Na^+ were almost unchanged for all of these electrodes. An additional emf behavior observed was that all electrodes using F–I exhibited a slow response to Li^+ . The electrode based on E exhibited a fast response to Li^+ as well as Na^+ and reached a steady potential within 30 s. On the other hand, the electrode using

I exhibited a slow response to Li^+ but not to Na^+ . Similar emf response behaviors were observed in all the electrodes based on E–I. These results suggest that it is difficult to form Li^+ complexes with the model II type molecules E–I, indicating slow kinetic reactions in their complexation with Li^+ . From these results it can be concluded that the model II type compounds are not a suitable design for obtaining a higher as well as an optimal Li^+ -selective ionophore, but this conclusion does not apply to all 14-crown-4-based compounds. In order to introduce double blocking walls into the base 14-crown-4 according to the model II type ionophore design, a bulky subunit should be used for one and a moderate unit for the other. J was designed according to this consideration, which used (dibenzyl)oxy)methylethylene as one of the moderate bulky subunits. Thus, the electrode based on J showed high Li^+/Na^+ selectivity of $\log K_{Li,Na}^{pot} = -2.8$. This selectivity value is obviously higher than that of the electrode based on B ($\log K_{Li,Na}^{pot} = -2.6$) which is one of the model I type compounds that contained tetramethylene, the same subunit as in J. Furthermore, the electrodes based on K and L did not show such slow response behavior to Li^+ as observed with the electrodes based on F–I. K has one bulky spiro ring unit of norbornene and one diethyl unit at the center carbons of the propylene-bridge sections of the base crown ring. However, the Li^+/Na^+ selectivity of the electrode based on K was 80 ($\log K_{Li,Na}^{pot} = -1.9$) and the ion selectivities for alkali metal and alkaline earth metal cations were almost the same as those with the electrode using the commercially available highly Li^+ -selective ionophore, dibenzyl-14-crown-4,⁵ which contained two benzyl side chains at the center carbon of the propylene-bridge section of the base ring. From these results it can be concluded that a compound with a bulky subunit or side chain at the center carbon of the propylene-bridge section is less effective than those with the subunit at the

Table I. Ion Selectivity Factors ($k_{Li,j}^{pot}$, j = Interfering Ion) for the Electrodes Based on 14C4 Derivatives

ionophore	$j = Na^+$	$j = K^+$	$j = Rb^+$	$j = Cs^+$	$j = NH_4^+$	$j = Mg^{2+}$	$j = Ca^{2+}$	$j = Sr^{2+}$	$j = Ba^{2+}$
A	-0.9	-1.2	-1.5	-1.6	-1.9	-4.2	-4.1	-4.2	-4.2
B	-2.6	-2.9	-3.0	-3.0	-3.0	-5.3	-4.7	-5.0	-5.0
C	-2.8	-3.3	-3.7	-3.6	-3.7	-6.1	-5.2	-5.0	-5.0
D	-2.9	-3.4	-3.6	-3.7	-3.5	-5.0	-5.0	-5.1	-5.0
E	-3.0	-3.6	-3.6	-3.5	-3.7	-5.0	-4.9	-5.0	-5.0
	(-3.1)	(-3.6)	(-3.7)	(-3.6)	(-3.8)	(<-5.0)	(<-5.0)	(<-5.0)	(<-5.0)
F	-1.9	-2.1	-2.3	-2.5	-2.5	-2.8	-2.9	-2.8	-2.9
G	-2.5	-3.2	-3.4	-3.5	-3.4	-4.3	-4.9	-4.9	-5.2
H	-2.3	-3.0	-3.2	-3.1	-3.0	-4.0	-4.2	-4.2	-4.1
I	-2.0	-2.7	-2.8	-2.5	-3.0	-4.2	-5.0	-4.7	-4.7
J	-2.8	-3.7	-3.5	-3.3	-3.5	-5.0	-3.9	-4.7	-4.7
K	-1.9	-2.0	-2.0	-2.0	-2.0	-5.0	-4.1	-4.5	-4.4
L	-2.4	-3.0	-3.2	-3.3	-3.2	-5.5	-5.2	-5.5	-5.4

^a Data obtained by the separate solution method (0.1 M cation chloride^{21,22}). Values by the fixed interference method ($j = 0.15 M^{21,22}$) are given in parentheses.

ethylene-bridge section of the base 14-crown-4. L has one diethyl unit at the center pivot carbon and one 1,1,3,3-tetramethylpropylene at the propylene-bridge sections of the base ring. The Li^+/Na^+ selectivity of the electrode with L was 250 ($\log k_{Li,Na}^{pot} = -2.4$), which is much higher than that of K ($\log k_{Li,K}^{pot} = -1.9$). The base 14-crown-4 has two kinds of methylene carbons; one is the carbon directly attached to oxygen ($-C-O-$) and the other is the center carbon in the propylene-bridge section ($-C-C-C-$). This selectivity difference between L and J suggests that the introduction of the "blocking" side chain or subunit to the C-O carbon (the carbon close to the donor oxygen) has more of an effect on Li^+ selectivity than introduction to the center carbon in the propylene-bridge section. This conclusion is logical judging from Li^+/Na^+ selectivities of all the synthesized compounds (see Figures 2 and 4).

The ion selectivity factors ($k_{Li,j}^{pot}$) of the electrodes based on the 14-crown-4 derivatives discussed here are summarized in Table I. Among all the electrodes using 14-crown-4 derivatives A-L, the best Li^+/Na^+ selectivity ($\log k_{Li,Na}^{pot} = -3.0$ (-3.1 by FIM)) was obtained using one of the model I type ionophores, E, which has a decalin subunit at the ethylene-bridge section of the base crown ring. The introduction of a long alkyl chain of *n*-tetradecyl in the decalino-crown compound E hardly affects its ion selectivity compared with those possessing no alkyl chain.¹⁰ In this case for the introduction of a long alkyl chain into the decalino-14-crown-4, which can add a high lipophilicity to the ionophore molecule itself, the introduction number should be 1. If two long alkyl chains were introduced into the crown ether compound, the Li^+/Na^+ selectivity must be poor compared with that of E, which has one long alkyl chain. This can be judged by comparing the selectivity values for E and I or C and G. The long alkyl chain can also be added at the center carbon of the propylene-bridged section of the decalino-14-crown-4. In this case, judging from the ion selectivity values for K and L, the Li^+/Na^+ selectivity would not be affected by the introduction of a long alkyl chain. This decalino-crown derivative is, however, hard to obtain in view of the organic reaction because the two C-O carbons in the decalin subunit are both quaternary.

As shown in Figure 2, the Li^+ selectivity of the best electrode based on E against alkali metal cations except Na^+ has similar values of -3.5 to -3.7 for logarithmic ion selectivity factors ($\log k_{Li,j}^{pot}$). This suggests that the limiting value of the Li^+ selectivity against alkali metal cations with 14-crown-4-based compounds is $\log k_{Li,j}^{pot} = -3.5$ to -3.7. However, to date the Li^+/Na^+ selectivity, $\log k_{Li,Na}^{pot} = -3.1$ to -3.3 (by FIM), observed with the decalino-14-crown-4 (E and the compound in ref 10) is the best value of all the 14-crown-4 derivatives

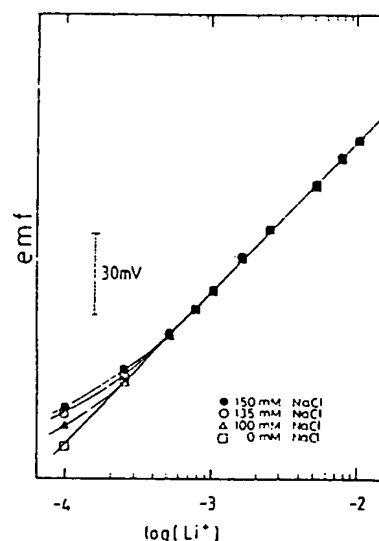


Figure 5. Typical Li^+ response curves of the electrode based on E with different Na^+ background concentrations.

developed.^{10,11} Some highly Li^+ -selective electrodes were reported in which a small addition of an electron donor compound such as tris(2-ethylhexyl) phosphate (TEHP) or trioctylphosphine oxide (TOPO) in the electrode membrane can improve their Li^+/Na^+ selectivity.^{5,7} However, a positive effect was not observed with the electrode based on E and TEHP or TOPO. Furthermore, the emf value for a 0.1 M Li^+ obtained with the electrode using I, which also possessed one decalin subunit, was smaller than that with the electrode based on E; whereas the emfs for a 0.1 M Na^+ with these electrodes were both almost the same value. These results suggest that for 14-crown-4-based compounds the limiting Li^+/Na^+ selectivity value is 1200–2000 ($\log k_{Li,Na}^{pot} = -3.1$ to -3.3) but does not exceed 3200 ($\log k_{Li,Na}^{pot} \geq -3.5$).

As an application of the electrode using E, the Li^+ determination was tested with artificial serum samples including Li^+ in the therapeutic concentration range (0.5–15 mM Li^+)¹ for manic-depressive patients. The typical Li^+ response curves are shown in Figure 5, where the background ion concentrations of the test solutions were varied with different concentrations of Na^+ (0, 100, 130, and 150 mM Na^+). The results reveal that the electrode based on E can determine 0.5 mM Li^+ having an error between 1.7% and 3.4% in the case where the background Na^+ concentration varies in the range from 130 to 150 mM and from 100 to 150

mM, respectively (the linear Nernstian response slope was observed in the concentration range from 2×10^{-6} to 1 M Li^+ without any interfering ions and up to 1 mM Li^+ when the test samples contained 150 mM Na^+). The 14-crown-4 derivative E presently offers the best Li^+ -selective electrode.

In this report, our intention was to create highly Li^+ -selective ionophores for an ion-selective electrode. The discussion on the ionophore chemical structures and their ion selectivities is also applicable as general knowledge of all the 14-crown-4 derivatives as relates to host-guest chemistry.

ACKNOWLEDGMENT

Partial support of this work by the Saneyoshi Scholarship Foundation, Shorai Foundation, and a Kurata Research Grant is gratefully acknowledged.

RECEIVED for review May 26, 1993. Accepted September 1, 1993.*

* Abstract published in *Advance ACS Abstracts*, October 15, 1993.